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Factors Initiating the Development of Acute Ischemic Cerebrovascular Accident in Young People

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Abstract: This article provides information about the main clinical and structural cerebral factors in the development of acute ischemic stroke in young. Ischemic stroke in young people has its own features. Risk factors for the development of the disease, pathogenetic mechanisms, clinical course and prognosis differ significantly from those in middle-aged and elderly patients, which determines the relevance of further study of this pathology.

Key words: acute ischemic stroke, young people, macro- and microstructural cerebral factors, antioxidant system, thrombolysis.

Cerebrovascular pathology, in particular stroke, remains one of the most pressing medical and social problems of modern medicine to this day and ranks third, and in some countries second, in morbidity and mortality after cardiovascular and oncological diseases. [1,2]. Given the persistent trend towards rejuvenation of diseases, stroke in young people is of greatest interest to scientists and doctors. [1,2,3]. According to literary data, the incidence of stroke in young people averages 3–23 cases per 100,000 population, which is 2.5–10% of all strokes, and this figure is growing steadily every year. [2]. This is due to the fact that risk factors for strokes that are common in the elderly are not identified in young people, and the pathogenetic mechanisms of development and clinical course of the disease have not been fully studied, and diagnostic and treatment algorithms have not been finalized. [1,2].

The problem of identifying the etiology that influences the development of ischemic stroke in young people is being studied by scientists from various fields of medicine. Numerous studies by scientists have made it possible to identify a number of causes that significantly influence the development and clinical course of ischemic stroke in young people, among which a special place is occupied by dissection of cerebral vessels, coagulopathy, antiphospholipid syndrome, hyperhomocysteinemia, mitral valve prolapse, genetic predisposition, etc. [3].

As the analysis of literature has shown, the features of the influence of macro- and microstructural cerebral factors on the neurological and functional status of young patients in the acute period of strokes have not been fully studied to date, and predictors of an unfavorable course of the acute period of stroke have not been sufficiently studied.

In this regard, clinical and neurological studies have not lost their relevance to this day, since a small lesion may not be detected during neuroimaging diagnostic methods, but may give pronounced neurological symptoms. In the first stage, clinical studies allow us to determine the impact of symptoms on the functional status of patients, assessing the degree using the National Institutes of Health Stroke Severity Scale, Rankin, Barthel or other scales, with subsequent differentiation of stroke from other diseases [4].

Also at this stage it seems possible to establish the pathogenetic subtype of ischemic stroke with further determination of patient management tactics. The generally accepted classification of pathogenetic subtypes of ischemic stroke today is the TOAST classification, according to which atherothrombotic, cardioembolic, lacunar, stroke of other established etiology and stroke of unknown etiology are distinguished. [1,2,6].

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Recently, neuroimaging biomarkers of macro- and microstructural cerebral reserve have acquired considerable significance in the diagnosis of strokes, among which hypoperfusion can rightfully be attributed, which takes direct part in the development of the pathohistological and neuroimaging phenomenon. [7]. According to MRI studies, this phenomenon is manifested by acute lacunar infarctions, lacunae, white matter hyperintensity, dilation of perivascular spaces, and cerebral microbleeds. N.A. Kailova also considers the microscopic integrity of the brain as a marker of cerebral reserve, explaining this by the fact that pathological aging of the brain in patients with vascular risk factors and diseases is characterized by a decrease in the integrity of some strategic tracts. [7,8].

Also, from a diagnostic point of view, biochemical markers of cerebrovascular accidents and changes in hemostasis, in particular the antioxidant system, which results in endothelial dysfunction and endogenous intoxication, are of great importance.

According to Kulesh A.A., the discovery of successive stages of ischemic brain damage led to a deepening of understanding of the complexity, dynamism, interconnection and cascade nature of the biochemical reactions underlying it. [8].

As is known, the degree of damaging effect of ischemia is determined, first of all, by the depth and duration of the decrease in cerebral blood flow. In response to ischemic damage to brain tissue, polymorphonuclear leukocytes begin to adhere to the vascular endothelium, and local inflammation develops, causing obstruction of small vessels. Fibrinolytic activity of the blood is suppressed, the zone of the infarct core expands, and new areas of ischemic penumbra are formed. In parallel, processes of free radical oxidation and acidosis occur, leading to the development of reactive hyperemia in the area of the ischemic penumbra and the formation of vasogenic cerebral edema. [8,9,10]. The processes of lipid peroxidation (LPO) and NO synthesis are activated with the depletion of the endogenous antioxidant defense system, contributing to the development of oxidative stress, which, when interacting with the ischemic cascade, causes a mutually reinforcing effect. [8,9].

At the same time, stimulation of neurotrophic processes occurs. Neurotrophy is a natural response that manifests itself through proliferation, migration, differentiation and survival of cells and is characterized by regeneration processes. In these neurotrophic processes, the main role is given to neurotrophins, which are regulatory proteins of the nervous tissue. Neurotrophins determine the plasticity of neuronal tissue and participate in the processes of restoration of impaired functions of neurogenesis [10].

Currently, of greatest interest to us among all neurotrophins is the brain-derived neurotrophic factor (BDNF), which is a key mediator of neuronal survival and restoration. [11]. BDNF was isolated from brain extract and first described in 1987. BDNF is a protein that is synthesized in the endoplasmic reticulum as a precursor protein (pro-BDNF), undergoing editing in the Golgi complex to form biologically active mature BDNF (mBDNF). Mature BDNF innervates the tropomyosin tyrosine kinase B receptor (TrkB), which triggers phosphorylation cascades leading to protein synthesis, axon growth, dendritic maturation, and increased synaptic plasticity. [12]. Decreased circulating BDNF levels increase the risk of stroke, and low serum BDNF concentrations in the acute period are considered to be a factor in poor prognosis of the patient's functional status, as confirmed by studies by Stanne et al (2016) [11, 12].

Also of no small interest in the pathogenesis of ischemic stroke in young people is homocysteine - a sulfur-containing amino acid synthesized endogenously from methionine. It is a powerful antioxidant, plays a huge role in the formation of disulfide bonds in proteins of the connective tissue matrix, is one of the main sources of sulfides and is necessary in metal metabolism. Increased homocysteine circulation is observed due to deficiency of B vitamins and folate, as well as genetically determined defects in some enzymes involved in the folate cycle. Hyperhomocysteinemia leads to damage to the tissue structures of the arteries, initiating the release of cytokines, cyclins and other inflammatory mediators; to loosening of the arterial walls; the formation of local defects in the endothelium and, accordingly, to the deposition of cholesterol and calcium on the vascular wall.

P.M. Kanani and co-authors have shown that increased homocysteine levels also provoke oxidative stress, disrupt endothelial function and increase thrombogenic activity of the blood, which together leads to the development of atherosclerosis, which is one of the causes of ischemic stroke. [12]. Confirmation of this can also be found in the work of Pizova N.V. and co-authors (2017), which determined the role of homocysteine as a potential procoagulant and its ability to inhibit antithrombin III, protein C and activate factors V and XII, which play an important role in the development of the cardioembolic subtype of ischemic stroke. Pizova N.V. and co-authors also point to the association of increased homocysteine levels with an increased risk of developing ischemic stroke and to the role of mutations in the MTHFR gene, on which more than 40 point mutations or point nucleotide polymorphisms have been found. (Single Nucleotide Polymorphisms, SNPs) [13].

An important role in the development of ischemic stroke is played by thrombosis, which can be a consequence of acquired and hereditary genetic mutations of blood clotting factors. Timchenko L.V. and co-authors identified the most common gene markers of hereditary thrombophilia, among which the most interesting are the C677T mutation in the MTHFR gene, the FV Leiden mutation - risk factors for the development of venous and arterial thrombosis and the G20210A mutation in the prothrombin gene [2].

To date, the role of gene networks in the development of stroke has been determined, but the associations of various polymorphisms of candidate genes for acute ischemic stroke at a young age have not been sufficiently studied, so the study of the molecular genetic basis for the development of strokes is of particular interest. Interpretation of the mechanisms of phenotypic realization of individual polymorphic genes and gene networks is difficult, since it does not always have direct clinical, biochemical and hemostasiological markers. [14,15].

According to Kolchina, genes of apolipoproteins, enzymes and lipid metabolism receptors can be rightfully considered as candidate genes for ischemic stroke. At present, the most promising direction in the study of genetic hereditary predisposition to stroke is the analysis of associations of polymorphic DNA loci with the risk of disease. [14].

Thus, there is a clear relationship between risk factors, biochemical and genetic markers of the development of pathological processes in the brain, which plays a decisive role in the choice of treatment tactics. A thorough study of risk factors, clinical and neurological features, biochemical and genetic markers of brain damage will allow us to select high-quality therapy and develop a program for predicting and secondary prevention of stroke, which will, in turn, significantly reduce the percentage of mortality and disability.

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